Use of Recombinant FVIIa for Intraperitoneal Coagulopathic Bleeding in a Septic Patient

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Recombinant activated coagulation factor VII (rFVIIa) is a U.S. Food and Drug Administration (FDA)-approved drug for use in hemophiliacs with inhibitors.[1] It has been safely utilized in this population of patients for over 13 years. rFVIIa functions by increasing local thrombin generation at sites where endothelium is damaged, resulting in increased platelet activation and aggregation and enhanced fibrin deposition.[2] Because of its localized action at the site of endothelial damage, it is now being used in treating patients with an acquired coagulopathy.[3]

The emergency use of intravenous adjuncts for hemorrhage control, other than standard component therapy, has been largely ignored in the massively bleeding surgical patient.[4] An injectable substance that would enhance normal clotting might reduce deaths from uncontrolled hemorrhage, decrease units transfused along with their complications, and reduce expense. Several drugs (estrogens and anti-fibrinolytic agents) have been utilized to decrease bleeding during elective surgery, but rFVIIa holds more promise.[4] rFVIIa was originally isolated and later produced by recombinant technology to treat hemophilia patients with inhibitors to factors VIII and IX during critical bleeding episodes or major surgery.[5] It also corrects the platelet defects associated with Glanzmanns thrombasthenia, Bernard–Soulier syndrome, uremia, and other severe congenital and acquired thrombocytopathias.[6-8] Furthermore, it has been shown to rapidly reverse coumadin anticoagulation in healthy volunteers and to correct prothrombin times in cirrhotic patients.[9-11] The widening clinical indications for rFVIIa are suggested by recent published descriptions of reduced blood loss in many previously normal surgical patients. These include patients undergoing orthotopic liver transplantation, massive gastrointestinal bleeding, exsanguinating trauma, cirrhosis, bone marrow transplant, heart valve replacement, amniotic embolus and disseminated intravascular coagulation (DIC), transabdominal retropubic prostatectomy, and Dengue hemorrhagic fever with DIC.[12-23] We report here the use of rFVIIa utilized to control diffuse bleeding from the retroperitoneum in a septic patient with DIC from necrotizing pancreatitis.

KEY WORDS: FVIIa, coagulopathy, sepsis, pancreatitis

CASE REPORT

A 45-year-old man was transferred to our institution with a 2-week history of alcohol-induced necrotizing pancreatitis and resultant respiratory and renal failure. Seventeen days into his hospitalization, he deteriorated clinically, exhibiting fever, tachycardia, and abdominal distention. Repeat computed tomography revealed an enlarging peripancreatic fluid collection that was aspirated. Despite negative cultures, the patient's clinical course continued to deteriorate, leading to an exploratory laparotomy and debridement of the infected pancreatic necrosis. During the initial operation, the patient became hypothermic, acidotic, coagulopathic, and manifested septic shock, necessitating initiation of vasopressors and massive transfusion (Table 1). Despite adequate intravascular volume, he required perioperative pressor agents, including levophed (0.5 mcg/kg/min), epinephrine (0.3 mcg/kg/min), and vasopressin (0.4 units/min). Coagulopathic bleeding from DIC related to sepsis was manifested by oozing from various intravenous sites. After adequate pancreatic debridement, his retroperitoneum was packed with gauze sponges and his skin closed.

Over the subsequent 10 hours, the patient received 19 units of packed red blood cells (PRBC), 36 units of platelets, and 12 units of fresh frozen plasma (FFP). Despite the aggressive transfusion on the day of surgery, the patient's hemoglobin and platelet count continued to fall. Due to the failure of standard component therapy, and the patient's worsening condition, a single dose of 120 μg/kg of rFVIIa was given intravenously. Clinically, the patient stopped bleeding and hemodynamically stabilized, manifested by his decreasing requirement for pressor agents. Within 2 hours of injecting the rFVIIa, the patient's laboratory values were markedly improved (Table 1). Shortly thereafter, he developed abdominal compartment syndrome,

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TABLE 1. Coagulation Data Immediately Before and After Giving a Single 120-μg/kg Dose of rFVIIa, With Follow-up Values 24 Hours Later. Blood and Component Data Before rFVIIa Is for the Preceding 10 Hours

	°C	PT/PTT	Hgb	plt	Fib	PRBC	FFP	Plt units	pH	BD
Before rFVIIa	34.1°	18.8/55.7	6.2	60	119	19	12	36	7.23	−10
2 hrs after rFVIIa	36.8°	9.5/36.5	9.8	109	156	0	0	0	7.32	−6
24 hrs after rFVIIa	36.1°	11.1/33.2	9.2	153	220	1	4	6	7.27	−7

requiring opening of his abdomen in the intensive care unit. No evidence of ongoing fresh intraperitoneal hemorrhage was discovered, only bowel wall edema. Over the ensuing 24 hours, the patient's blood product requirements decreased and his coagulation status stabilized (Table 1). After a prolonged hospital course marked by multiple organ failure (MOF), acute renal failure, dialysis, and multiple operative pancreatic debridements, the patient ultimately survived with recovery of his renal function and was discharged from the hospital.

DISCUSSION

This case demonstrates the potential usefulness of rFVIIa for rapidly controlling the diffuse bleeding of an acquired coagulopathy in a profoundly septic patient with DIC from necrotizing pancreatitis. Management of patients with pancreatic abscess revolves around surgical debridement.[24-25] Patients taken for operative debridement of the necrotic pancreas not infrequently develop hemorrhagic (18%) and septic complications.[26] These patients frequently have very high incidence of MOF (85%), prolonged intensive care unit stays and undergo multiple operative procedures.[27] Overall mortality ranges from 6% to 33% with 1 large series reporting an average of 17%.[28] The patient presented in this report manifested most of the complications associated with pancreatic sepsis and necrosis.

The acquired coagulopathy after severe sepsis is resistant to standard blood product replacement, and usually it is only reversed when the septic process resolves. However, with the availability of new injectable hemostatic agents, it may respond to drug therapy. Furthermore, it appears that rFVIIa rapidly reversed the coagulopathy of hypothermia.[27-34] No complications were attributed to the use of rFVIIa. This case suggests a role for the use of rFVIIa in the treatment of the acquired coagulopathic bleeding associated with sepsis-induced DIC and hypothermia.

When bound to exposed tissue factor (TF), normally expressed FVIIa initiates activation of the extrinsic clotting system at the site of vessel injury without causing systemic hypercoagulability.[3] rFVIIa is an attractive candidate therapy for treating coagulopathy because it bypasses much of the intrinsic coagulation system, is only active in the presence of exposed TF, and has a rapid onset and a short half-life. Tissue factor is not normally expressed in the intact vascular space but exists in high concentrations in the media and becomes exposed only upon vessel injury.[35] Tissue factor levels can be increased on the surface of activated white blood cells, especially after sepsis; however the significance of this is unclear as activated TF levels (the biologically functional form of the molecule) have not been measured.[3]

The lethal triad of hypothermia, coagulopathy, and acidosis was described in trauma patients but has been recognized in patients with massive bleeding from nontrauma causes.[36] Similarly, abdominal compartment syndrome occurs in patients with either massive intrabdominal bleeding or severe reperfusion injury from any cause.[37-40] The patients suffering these complications usually have been massively transfused and resuscitated. Trauma patients undergoing damage control maneuvers have at best a 60% survival, with the nontrauma patients experiencing a somewhat worse outcome.[41] New methods of hemorrhage control may serve to ameliorate some of these complications. Combining new hemostatic approaches with conventional damage control methods is a potentially beneficial area of clinical research.

Five placebo-controlled animal studies have been completed evaluating the role of rFVIIa as a hemostatic agent in previously normal animals with severe liver injuries.[42-46] These studies include different combinations of liver injuries, resuscitation strategies, and dose regimens. Three studies were in warm animals where the rFVIIa was the only hemostatic agent utilized.[44-46] One of these experiments demonstrated a decrease in blood loss, whereas the other 2 documented a favorable response in blood pressure. The other 2 studies were completed in cold and dilutionally coagulopathic animals with grade V liver injuries.[42,43] rFVIIa was used as an adjunct to gauze packing, much as described in the current case report. These 2 animal studies demonstrated a greater than 45% decrease in blood loss in the rFVIIa-treated animals. None of the animals in any of the controlled studies demonstrated any evidence of large vessel, microscopic thrombi, or any complication attributed to rFVIIa.

Patients that initially survive massive hemorrhage and sepsis may ultimately succumb to MOF.[47] Hardaway and Gando have described the possible relationship between diffuse microthrombi and organ failure.[48-50] It is theoretically possible that modulation of the coagulation cascade to improve local hemostasis could result in an increased incidence of late MOF due to increased microthrombi formation and fibrin deposition. Although the focus of the controlled animal studies was appropriately on the initial hemorrhage control aspects of rFVIIa, none of the animal studies have demonstrated any evidence of increased thrombotic complications or other safety concerns. The theory that systemic delivery of rFVIIa will cause increased diffuse microthrombi has not been supported by the animal

data. The growing body of human data in nonhemophiliac patients does not describe significant thrombotic complications; however, with no control groups, these data must be considered suggestive.

An increasing number of published case reports document the use of rFVIIa in a variety of patients with an acquired coagulopathy. We have added to this growing body of literature a septic patient with DIC and retroperitoneal bleeding after a necrosectomy for necrotizing pancreatitis. To date, there seems to be a paucity of data documenting adverse outcomes attributable to the drug. Several authors have reported their experience with thrombotic events (MI and stroke) with the systemic use of rFVIIa.[53,54] In the 13 years rFVIIa has been clinically used, few documented cases of MI have occurred, supporting the claim that a limited number of thromboembolic events have resulted from widespread use.[3,55,56]

SUMMARY

In conclusion, over the last 18 months, 5 different large animal studies have been performed, 3 utilizing rFVIIa as a single agent and 2 as an adjunct to standard therapy. Three of 5 studies demonstrate a decrease in blood loss, whereas none of the studies reveal any evidence of microthrombi.[42-46] A series of human case reports has described the potential usefulness of this drug in patients with coagulopathic bleeding from a wide variety of causes.[12-23] We describe herein a septic patient with DIC from necrotizing pancreatitis successfully treated with a single dose of rFVIIa. Currently, rFVIIa is being utilized off label in patients that demonstrate an acquired coagulopathy from a variety of causes. At this point, the results seem promising with no overwhelming complications described. However, without an appropriate control group, any definitive conclusions are premature. A prospective, randomized, and blinded human trial is urgently required to answer the provocative questions raised by the preclinical studies and the growing number of patients with an acquired coagulopathy treated with rFVIIa.

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